REMARKS

Applicant respectfully requests the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims

Claims 1-8 are currently pending in the present application. The Office Action is non-final. Claims 2-6 have been amended without prejudice or disclaimer. No new matter has been added by way of amendment. Support for amended claims 2-6 can be found at pages 6-8 of the present specification. Thus, no new matter has been added.

Based upon the above considerations, entry of the present Amendment is respectfully requested.

Issues Under 35 U.S.C. § 103(a), Obviousness

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) as obvious over Christensen *et al.* U.S. Patent No. 3,912,743 (hereinafter "the '743 patent"), supplemented with Christensen *et al.*, "*Antidepressant and Parkinsonism- inhibiting 3-[(alkyloxy- or aryloxy)methyl]-4-phenylpiperidinies*," document CA 81:152011 (hereinafter "CA 81"), in view of Kozikowski *et al.*, U.S. Patent No. 6,180,648 (hereinafter "the '648 patent") and Moldt *et al.*, U.S. Patent No. 6,376,673 (hereinafter "the '673 patent"), supplemented with Moldt *et al.*, "*Preparation of Piperidine Derivatives as Neurotransmitter Re-Uptake Inhibitors*," document CA 130:13920 (hereinafter "CA 130") and Watjen, F., "*A Preparation of Novel Piperidine Derivatives, Useful*

as Monoamine Neurotransmitter Re-Uptake Inhibitors," document CA140:406740 (hereinafter "CA 140").

The Examiner asserts that the '743 patent discloses 4-substituted phenyl piperidinyl compounds which are made from the intermediates having the CH_2-OR^c moiety at the third position of the piperidinyl ring. The Examiner also suggests that the difference between the present invention and the compounds of the '743 patent is that instead of a single halogen substituted at the 4-position of the 4-phenyl ring, the claims of the present invention have 3,4-dihalogen substitution.

The Examiner also asserts that the '648 patent and Moldt are directed towards compounds that the 4-phenyl substituents can be optionally multiply substituted. Also, the Examiner alleges that the '743 patent, '648 patent and Moldt are all analogous art of antidepressant compounds having the 4-substituted phenyl piperidine core.

The Examiner also asserts that a skilled artisan in possession of the above references is in possession of the instant claims since it is well recognized that the dichloro-substituted 4-phenyl piperidines would be expected to have similar antidepressant activity of the proven compounds disclosed by the prior art. In making this assertion, the Examiner indicates that providing the starting material (3,4-dichlorophenyl-3-CH_2OH-piperidine) and the "proven" process of transforming the 3-CH_2OH-piperidinyl compound to 3-CH_2-OR (see the '743 patent at col. 3, lines 15-33) would place the instant claims in the artisan's possession. Applicant respectfully traverses.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires

consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. But before the Examiner can utilize these guidelines, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*; *supra*. To reject a claim based on the above mentioned guidelines, the Examiner must resolve the *Graham* factual inquiries. MPEP § 2143.

If the Examiner resolves the *Graham* factual inquiries, then the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 sets forth the rationales that were established in *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Applicant respectfully submits that the Examiner has not appropriately resolved the *Graham* factors, including the factors of determining the scope and content of the prior art and ascertaining the differences between the prior art and the claims that are at issue. Based on the following, Applicant maintains that the above mentioned *Graham* factors actually reside in Applicant's favor. Additionally, Applicant submits that since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides for combining the cited references is improper.

Applicant respectfully submits that the present invention is distinct from the cited references and that the Examiner is basing the Examiner's assertions on hindsight reconstruction.

The instant invention

The compounds of the present invention have been developed in order to provide new compounds with an optimized biochemical profile in regards to activity of reuptake of the monoamine neurotransmitters serotonin, dopamine and noradrenaline. An example of this type of biochemical profile is the ratio of the serotonin uptake versus the noradrenaline and dopamine activity (see the present specification at page 1, lines 25-28). Applicant submits that the present invention shows unexpected advantageous results as compared to the compounds of the prior art.

Differences between the invention and the prior art

The '743 patent

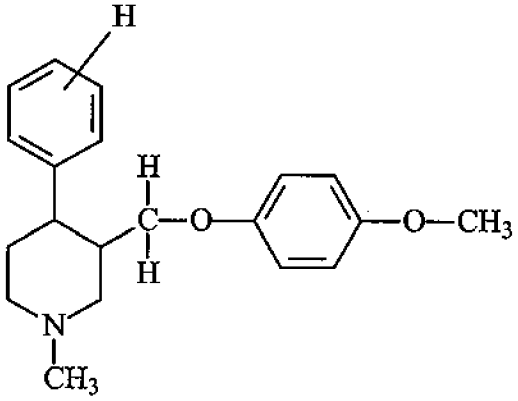
The '743 patent describes 4-phenylpiperidine compounds being useful as antidepressant and anti-Parkinson agents (CA81, also discloses compounds having a chemical structure, which are closely related). The '743 patent describes about 61 compounds, which have been prepared by one of the three methods mentioned in the patent. The '743 patent states that the compounds can be used as antidepressants and anti-Parkinson agents. Three compounds (the compounds designated GF 04, GF 09 and GF 44 within the tables located beneath columns 6 and 7 of the '743 patent) are closely related to the compounds of the present invention, in that only a halogen atom in the 3-position of the phenyl group needs to be incorporated in order for the compounds to fall within the scope of the present invention.

Within the disclosures of the '743 patent, however, of all the compounds indicated, activities for only eight of the compounds are mentioned (See the '743 patent tables beneath columns 8 and 9). The related compounds, GF 04, GF 09 and GF 44 are not among the compounds for which the activity has been investigated and published.

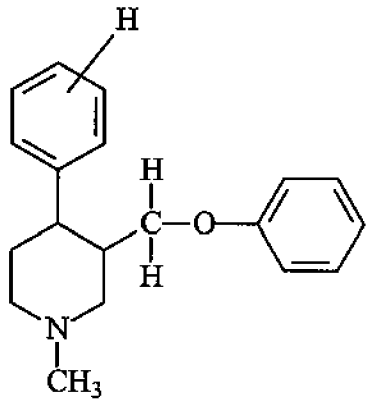
Consequently, the skilled person wishing to develop new active compounds would not be lead to investigate the activity for the compounds of the present invention, but would rather be motivated by the teachings of the '743 patent to those specific compounds within its disclosures that show promising biological and toxicological activity profiles. Furthermore, in the '743 patent, it is discussed that some of the compounds tested are especially strong inhibitors of 5-HT uptake, while others are more potent NA-uptake inhibitors. Hence, depending on the desired type of activity, the skilled artisan would start out with one of the compounds showing the desired type of activity. Additionally, as indicated in the tables located in column 9 of the '743 patent, if a skilled artisan chooses a particular activity compound, differences between very similar compounds also have to be considered. For example, the difference between compounds GF 48 (X=H(-)) and GF 49 (X=H(+)) show that the LD_{50} level for GF 49 is 6-fold higher than GF 48. Therefore, GF 49 would be more preferable lead compound based on toxicity considerations. This difference between GF 48 and GF 49 is an example of unpredictability in the art, which is one factor in showing non-obviousness.

Applicant provides as examples two compounds, GF 32 and GF 49 which the '743 specifically mentioned as having 5HT and DA uptake activity (See the '743 patent at column 7, lines 50-64 for GF 32, and column 8, line 62 to column 9, line 35, for GF 49; GF 49 was selected for overall IC_{50} activity vs. LD_{50} profile as described above).

The compounds reproduced below, Applicant submits, are the closest art that the '743 art provides.



GF 32 (5HT-Uptake Activity)
R= 4-Methoxyphenyl
X= H (+) form
R1 = Methyl
HCl Salt



GF 49 (NA and DA-Uptake Activity)
R= 4-Methoxyphenyl
X= H (+) form
R1 = Methyl
HBr Salt

The above compounds were mentioned in the text as having highly desirable characteristics of activity, lack more serious side effects (*e.g.*, GF 32), and are specifically claimed within claims 2, 3, 5 and 6 of the '743 patent.

The courts since *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), have recognized that inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty. Ltd.*, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007) (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound).

There "has to be are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Takeda*, *supra*, (citing *KSR*).

Applicant submits that since there is no disclosure, teaching, suggestion, reason or rationale provided in the '743 patent reference, a chemist would not look towards the compounds the Examiner has selected for guidance in preparing compounds of the present invention. Indeed, since there is no data regarding any biological activity for the compounds the Examiner selected, and due to unpredictability in the art (as exemplified above), Applicant submits that a chemist would be drawn to the compounds presented above for guidance out of all the compounds listed. Therefore, based upon the above, the '743 patent does not teach the compounds of the present invention.

The '673 patent

The '673 patent describes compounds which to some extent are related to the compounds of the present invention. Applicant submits that one major difference, however, is found with the R^3 group. In the '673 patent, the R^3 group is -CR'=NO", whereas in the present invention the R^3 group is $-CH_2-O-R^c$, where R^c represents alkyl or cycloalkyl. Within the '673 patent, only two compounds were tested, namely, 1-methyl-3-methoxyiminomethyl-4-(3,4-dichlorophenyl)piperidine (See the '673 patent, Table 1) and 1-methyl-3-methoxyimino-4-(3,4-dichlorophenyl)piperidine (See the '673 patent, Table 2). Applicant notes that the chemical difference between these two compounds is that the compound first mentioned contains one methyl group more than the second mentioned compound. As the tables indicate, the 5-HT-

uptake for each of these compounds, however, differs by over a factor of 100 in their IC_{50} values. This is another example of unpredictability in the art, which is a factor in showing non-obviousness. A chemist would not be able to predict that the same compound only differing by one methyl group would yield such a difference in IC_{50} values.

Therefore, Applicant respectfully submits that the skilled artisan wishing to develop new compounds having an improved biological effect, would be lead to investigate the importance of the chemical structure of the R^3 group in the compounds, as the '673 patent appears to teach that the biological activity of the compounds is closely related to the R^3 group.

Furthermore, Applicant submits that the '673 patent appears to be silent as to how the skilled artisan investigate the importance of the presence of a phenyl group substituted with two chloro atoms in the 3- and the 4-position, respectively. In order to reach the compounds of the present invention, Applicant submits that the above teachings would be a necessary change as compared to the compounds of the '673 patent. Therefore the silence of '673 patent as to how the skilled artisan investigate the importance of this matter is significant.

The '648 patent

The '648 patent describes a very large number of compounds (as well as CA 130 and CA 140 disclosing compounds having a chemical structure which are closely related). Of all the compounds disclosed, only 11 of these compounds, however, have been tested for their activity to inhibit the uptake of dopamine (See the '648 patent, column 11, Table 1). Applicant notes that the chemical structure of the compounds tested differs from the compounds of the present invention in two ways. First, the R^3 group is different than that of the present invention.

Second, the R^4 group is a phenyl group of a 4-chloro-phenyl group. Applicant again respectfully submits that in regards to the '648 patent, the skilled artisan would find no motivation within the '648 patent to add another substituent to the phenyl group in the 3-position, which would be necessary to reach the compounds of the present invention. On the contrary, as disclosed in the '648 patent at column 6, lines 42-43, it is stated that a preferred value for R^3 (corresponding to R^4 in the present invention) is 4-chlorophenyl, 4-florophenyl, 4-methylphenyl or 4-isophenylphenyl. Therefore, the teaching of the '648 patent will motivate the skilled artisan to exchange the chloro group in the 4-position with another group than the ones mentioned in the'648 patent in order to reach at improved compounds. Applicant submits that the skilled artisan would not at all be motivated to add a further substituent to the phenyl group or to incorporate it in the 3-position.

Applicant respectfully submits that none of the teachings contained in the documents cited by the Examiner (either taken as a separate teaching or in combination) would motivate the skilled artisan to investigate and subsequently develop compounds corresponding to the compounds of the present invention. Such compounds of the present invention are novel in that that they show an optimized biochemical profile with regards to activity on the reuptake of the monoamine neurotransmitters serotonin, dopamine and noradrenaline. An example of this type of biochemical profile is the ratio of the serotonin uptake versus the noradrenaline and dopamine activity. Applicant submits that the present invention shows unexpected advantageous results as compared to the compounds of the prior art.

Additionally, Applicant respectfully disagrees with the Examiner that the present invention would be obvious to the skilled artisan. Due the unpredictability in the chemical arts,

the particularly unique structure of the present invention, Applicant respectfully submits that the present invention is not obvious in light of the '743 patent and that the Examiner is applying hindsight reconstruction.

As indicated in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd. and Teva Pharmaceuticals USA*, 87 USPQ2d 1452 (Fed. Cir. 2008), the Court stated that:

> [T]he analysis of the third Graham factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a chemical compound, a *prima facie* case of obviousness requires "structural similarity between claimed and prior art subject matter...where the prior art gives reason or motivation to make the claimed compositions" (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))).

Additionally the Court also noted that:

> Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd. and Teva Pharmaceuticals USA, supra.*

As indicated previously, the courts since *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), have recognized that inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, ; *supra* (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound).

Applicant submits that obviousness based on structural similarity cannot be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (*i.e.* a lead compound) since the '743 patent does not specifically disclose a compound that could be considered a lead compound for comparison. As indicated above, if lead compounds were to be selected, it would be appear that based on the data disclosed in the '743 patent, compounds GF 32 and GF 49 would be the selected compounds, not the ones selected by the Examiner (*i.e.*, GF 04, GF 09 and GF 44). Applicant submits that the Examiner is using hindsight reconstruction based on the similarities of the compound moieties in the '743 patent to that of the present invention and not based on the teachings of the reference.

Since the '743 patent does not specifically disclose the compounds of the instant application, a chemist would not be motivated to modify the compounds of the '743 patent to make the present invention.

In light of the above presently amended claims and remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the '743 patent reference that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the same reference is incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established.

Since the present invention is not obvious in light of the '743 patent, the combinations of the '743 patent and the above references also fail. The secondary references, CA 81, the '648 patent, the '673 patent, CA 130, and CA 140 do not cure the deficiencies of the '743 patent. Therefore, the combinations of the '743 patent and the above mentioned references do not arrive

at the present invention. Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established for any of the above mentioned claims. Applicant respectfully requests reconsideration and subsequent withdrawal of the above rejection.

In view of the above remarks, Applicant believes the pending application is in condition for allowance.

CONCLUSION

A full and complete response has been made to all issues as cited in the Office Action. Applicant has taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicant respectfully requests that a timely Notice of Allowance issue for the present case.

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters within the present application that need to be resolved, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: DEC 1 2 2008

Respectfully submitted,

By #42,874

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